Firms should pursue narrow indications

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Of all the reasons that will be advanced for the disappointments surrounding the sepsis products of Centocor (Malvern, PA), Xoma (Berkeley, CA), and Synergen (Boulder, CO), the one that is most likely to be overlooked is the relationship between the drugs' activities, the companies' valuations as driven by analysts' projections of market size, and the companies' attempt to design clinical trials to address the largest possible market. This runs counter to the more well-established clinical strategy of pursuing the cleanest, narrowest, least-ambiguous indication to get a drug approved, and then broadening the indication with subsequent studies. For example, alpha interferon, whose clinical trials were managed by Hoffmann-La Roche (Nutley, NJ) and Schering Plough (Madison, NJ), was initially approved for hairy cell leukemia, then expanded to Kaposi's sarcoma, and then later expanded to treatment for hepatitis B.

Each of the sepsis drugs showed some evidence of efficacy in phase II trials. With Centoxin, there were case reports of dramatic improvement of children with meningococcemia treated with the compound. Although this represents a very small fraction of the potential sepsis market, a well-controlled phase III clinical trial in this defined patient subset might very well have been strikingly positive, and the drug might have been approved on this basis. Using the alpha-interferon paradigm, a second, larger, defined subset of patients could then have been tested with an already-approved drug, thereby gradually expanding the market. In the meantime, product sales would have been steadily mounting, and the company could have more easily weathered the storm if the broadest indication was not demonstrated on the first large-scale study.

The emergence of the biotechnology industry, and its voracious capital requirements that our private financial markets were ill-equipped to supply, spawned a new financial creature that has been called "public venture capital." Several hundred fledgling biopharmaceutical companies now participate in the public spectacle of quarterly reporting, public announcements of material information, and investor relations usually reserved for more financially mature organizations. The inexorable consequence is that the companies' clinical trials, from filing initial-new-drug applications through publication of phase III data, are performed in the glare of public scrutiny, so every hiccough is pounced upon by analysts trying to project values for investors.

Development of a drug, however, has its natural ebbs and flows. It would be interesting to speculate what would have happened to a biotechnology company developing a novel lipid-lowering drug had it had the same history as Merck's (Rahway, NJ) Mevacor. A precursor of that drug was well on its way through development when it hit an unexpected snag—unacceptable hepatic toxicity. It is testimony to Merck's management that it persevered and to its science that it solved the problem. Merck synthesized a derivative, and created Mevacor, a drug that improves lipid profiles for tens of thousands of patients and earns Merck over $1 billion.

Had this been a highly touted drug from a biotechnology company, however, at the public disclosure of the hepatic toxicity, analysts would have suddenly questioned the scientific basis of the technology, causing investor flight, resulting perhaps in the inability of the company to raise the capital to solve the problem and create a multibillion-dollar company. Yesterday's genius would become today's goat.

Immunex (Seattle, WA) is probably the most successful practitioner of defining patient subsets, no matter how small, in which a drug is most likely to work. Recognizing it was behind in the clinical development of its version of granulocyte macrophage-colony stimulating factor (GM-CSF), Immunex confined its initial phase III trial to the very narrow bone-marrow-transplant market. With a small patient number, and clear endpoints that were rapidly achieved, namely white-blood-cell count recovery associated with improved survival, Immunex literally leapfrogged its GM-CSF competitors and nearly beat Amgen's (Thousand Oaks, CA) granulocyte-colony stimulating factor (G-CSF) to the market. G-CSF's 10-to-one sales advantage can be attributed to its perceived superior characteristics, plus Amgen's installed sales force and marketing budget, more than the differences in indication. Immunex now has the "luxury" of amending its indication to encompass non-marrow-transplant chemotherapy, and its sales have clearly benefitted from physician recognition that a hormone that can accelerate white-blood-cell recovery in marrow transplants will work in less-intensive settings as well.

The reason this approach works better is that most diseases are more complex than we currently know. Therefore, broad categories are likely to include patients with different disease mechanisms that we currently group together without knowing it. For example, anemia was once considered to be one disease. We now know that it is not, and that treatment needs to be tailored for the underlying cause. Erythropoietin (EPO) would not work in B-12, folate, or iron deficiency anemias. If EPO's clinical trial had included these patients, the results would have been equivocal at best.

The question that will inevitably be raised is how analysts will respond to this corporate strategy. The best solution is for everyone to recognize that the lower-risk, smaller-initial-indication strategy is directly aligned with investor interest, and to build models based upon both lower costs of development and slower penetration into the larger markets. In fact, Immunex's projected valuation was never penalized for its narrow initial indication.

How much better might the biotechnology industry be regarded today if companies focused on getting their drugs approved first and worried about the more expansive indications later? ///